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ARTICLE

# Preserved speed of processing and memory in infants with a history of moderate neonatal encephalopathy treated with therapeutic hypothermia

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## Abstract

**Objective:** Survivors of neonatal encephalopathy (NE) are at risk for impaired cognition. The objective of this study was to assess speed of processing (SOP) and memory in infants with moderate NE.

**Study design:** Sample consisted of 17 infants with NE and 23 healthy controls. Visual-evoked potentials (VEP) were assessed at 8 months to assess SOP. Memory was assessed at 12 months using elicited imitation (EI). Memory and SOP had previously been assessed in this cohort in the newborn period.

**Results:** Infants with NE had similar SOP and EI performance as controls. Newborn SOP correlated with 8-month SOP in infants with NE, however, neonatal ERP memory measures were not correlated with EI performance at 12 months.

**Conclusions:** Infants with moderate NE treated with TH show preserved memory and SOP through 12 months. Early behavioral and electrophysiologic assessments of memory and SOP provide insight into developing cognitive functions in this risk group.

## Introduction

Neonatal encephalopathy (NE) occurs in approximately 2–6/1000 live births and remains an important cause of mortality and morbidity in children worldwide [1]. For many years, supportive care was the only treatment option available for infants with NE. In the early 2000s, based on the observation that hypothermia improves outcomes following cardiac arrest in adults, the first large clinical trials of therapeutic hypothermia (TH) for infants with NE were conducted. These studies demonstrated a reduction in death and disability in survivors of NE at 18–24 months [2–7], and at 6–7 years of age [8–10]. The primary outcome in these studies was a composite of death or disability, defined differently in the various studies but generally focusing on overall IQ scores and gross sensory/motor deficits.

However, studies conducted prior to the advent of therapeutic hypothermia point to specific impairments in cognitive functions such as memory [11, 12] and attention [13] in children with moderate NE who are considered unimpaired based on neurologic assessment. These children are more likely to be more than one grade level behind in school [14]. Subtle deficits in memory and attention could explain this diminished school achievement. Our group recently published data on memory function in 2-week-old infants who underwent TH after NE [15]. We found that after cooling, memory function, as assessed via event-related potentials (ERPs), was preserved; however, the topography reflecting processing differed between infants with NE and healthy control infants. Specifically, controls showed differences between novel and familiar stimuli in the left hemisphere solely, whereas infants with NE showed

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**Table 1** Baseline characteristics of participants

| | NE ($n = 16$) | Control ($n = 23$) | $p$ |
|---|---|---|---|
| Gestational age (weeks) | 40.02 (1.13) | 39.51 (1.04) | 0.16 |
| Birth weight (kg) | 3.78 (0.53) | 3.56 (0.37) | 0.18 |
| Male sex (%) | 75 | 52.17 | 0.19 |
| 1 min Apgar | 1.60 (0.91) | 7.83 (1.70) | **<0.0001** |
| 5 min Apgar | 3.80 (1.74) | 8.91 (0.29) | **<0.0001** |
| Maternal age (years) | 30.38 (4.70) | 34.17 (5.18) | **0.023** |
| White race (%) | 62.5 | 100 | **0.002** |
| Maternal education > high school (%) | 87.5 | 100 | 0.16 |
| Age at 8 month visit (weeks) | 36.36 (1.45) | 35.86 (1.20) | 0.27 |
| Age at 12 month visit (weeks) | 54.27 (2.99) | 53.80 (1.73) | 0.59 |

*Note*: Continuous variables expressed as mean (SD). Categorical variables expressed as percentage.

Bold values indicated statistically significant differences between groups

differences at midline, suggesting bilateral activation to achieve the task at hand. It is unclear whether or not this adaptation remains beyond the neonatal period and affects longer-term memory and neuronal processing.

Memory, attention, and other cognitive functions can be easily tested in verbal children older than 3 years using standard psychometric batteries. Though the development of cognition is quite protracted, and impairments are not readily apparent in daily functioning during infancy, it is possible to assess certain precursors to cognitive function earlier than 3 years of life, an important consideration given the large amount of brain development that occurs before that age. Speed of neuronal processing reflects processes such as myelination and synaptic efficiency, and is an underlying component of many cognitive processes. Speed of neuronal processing can be measured in infants using visual evoked potentials (VEP). Memory can be assessed in preverbal infants both electrophysiologically, using ERP, and behaviorally, using elicited imitation (EI) [16]. Evaluation of these functions longitudinally in infants who suffered from NE may allow us a better understanding of ongoing neural adaptations after brain injury. Further, early diagnosis of impairments allows for better targeted early intervention services and improved long-term outcomes in at-risk children.

The objectives of this study were to compare episodic memory function, speed of processing, and general development in survivors of moderate NE who underwent TH and healthy controls at various time points during infancy.

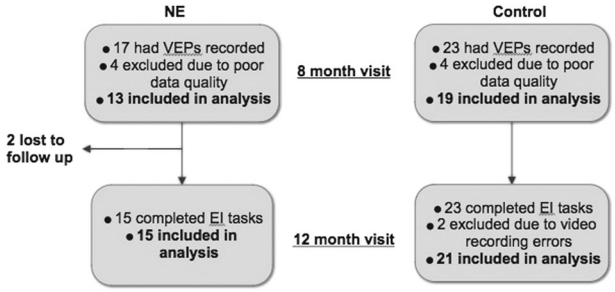


**Fig. 1** Flowchart of study participants

## Methods

### Subjects

Participants (study group) were recruited from the neonatal intensive care units at the University of Minnesota Masonic Children's Hospital, Children's Hospitals and Clinics of Minnesota–St. Paul, and North Memorial Medical Center. Control participants were recruited from the newborn nursery at the University of Minnesota Medical center. All participants were recruited from 2011–2014. We targeted a sample size of approximately 25 infants in each group, as other research using EI in this age group has found significant results with a similar sample size [17]. The Institutional Review Board at each hospital approved the study and parents provided written consent for participation of their infants.

Participant demographics are presented in Table 1. All participants were ≥36 weeks gestational age at birth. Study group participants were eligible if they were diagnosed with moderate NE (Sarnat stage 2), met criteria for and were treated with whole-body therapeutic hypothermia, and were discharged by 4 weeks of age. Control group infants were eligible if they had a 5-min Apgar ≥7 and remained healthy after birth. Exclusion criteria for both groups were the presence of a congenital anomaly or metabolic disease that would affect neurodevelopment, small for gestational age birthweight, and failure of the routine newborn hearing screen. Seventeen infants with moderate NE and 23 control infants met criteria, had parental informed consent for participation, and returned for follow-up to at least one of the study visits in late infancy (8 and/or 12 months). See flowchart (Fig. 1) for schematic of study participation. One infant in the NE group had unusable VEP data and did not return for the 12-month visit, therefore this participant was not included in analysis as there was no usable data from either visit. Therefore, 16 infants with NE were included in analysis of baseline characteristics (Table 1).

Enrolled infants participated in three study visits. At 2–4 weeks of age, they underwent auditory recognition memory assessment via ERP (described in detail in a

previous paper by our group) [15]. At 8 months, VEPs were assessed. At 12 months, general neurodevelopment was assessed using the Bayley Scales of Infant Development, third edition (BSID-III), and episodic memory was assessed using elicited imitation.

## Visual-evoked potentials

### Data collection

Infants were seated on a parent's lap in a darkened room during recording. The visual stimulus was a pattern-reversing black-and-white checkerboard, presented by E-Prime software (Psychology Software Tools, Sharpsburg, PA) with two reversals per second. The stimulus was displayed on a 20" ViewSonic Graphics Series G225f monitor (ViewSonic, Walnut, CA) for a total of 50 trials. Individual squares on the checkerboard measured approximately 1.5 × 1.5 cm, and the monitor screen was 39 cm wide × 29 cm tall, so that at a viewing distance of 60 cm the visual field subtended to 33.4° × 23.5°. A remote video system was used to monitor infants' attention to the screen, and the protocol was paused until attention was regained if there was a distraction. A research assistant hidden behind a cloth screen behind the monitor provided an auditory stimulus (squeak toy) as needed to keep the infants' attention on the monitor. This protocol has been used and described previously by our group [18]. Pattern-reversal VEPs were recorded from ongoing EEG using the Geodesic EEG System 200 (Electrical Geodesics, Eugene, OR). Sixty-four channel sensor nets are designed in a "geodesic" pattern, with a specific electrode placed at the vertex, allowing for consistent placement of the electrodes on the scalp of each infant. Nets are available in a variety of sizes to accommodate different head sizes. NetStation 4.4.2 software (Electrical Geodesics) was used to measure scalp impedances and accepted if <50 KΩ. EEG was referenced to the vertex, amplified with a 0.1 to 100 Hz bandpass, and digitized at 250 Hz.

### Data analysis

Data were analyzed offline using NetStation 4.4.2 software (Electrical Geodesics). Data were filtered with a 30-Hz lowpass filter, segmented to 500 ms periods starting 100 ms before stimulus presentation, and baseline corrected to the average prestimulus voltage. EEGs were hand-edited for poor recordings, eye movement, and movement artifact. Trials were excluded if >16% of electrodes were rejected. In acceptable trials, electrodes with bad data were replaced using spherical spline interpolation. Participants with fewer than 12 good trials per stimulus were excluded from further analysis. (Mean number of good trials: 31.4, range: 0–50). Four infants in the study group and 4 in the control group had their data rejected due to poor quality, leaving 13 NE and 19 control infants with usable data. For each participant with usable data, the average waveform at each electrode was calculated and re-referenced to the average reference. Latency to the peak of the P100 component was derived from a 90 to 200 post-stimulus window. When no P100 was identifiable in an individual lead, data were treated as missing in that infant. VEPs were analyzed from left (electrode 32), right (electrode 45), and midline (average of 37, 38, and 40) occipital lobe. See Supplementary Fig. 1 (online) for electrode placement.

## Elicited imitation

### Procedure

Individual test events were randomly drawn from a pool of 7 different events (Supplementary Table 1, online). Each infant was tested on 4 of the 7 events, events were counterbalanced across task and participants. Each event consisted of two target actions that when performed in the correct order produced a rewarding outcome (for example, assembling and ringing a gong).

During the testing sessions, after an initial period of free play to allow the infant to "warm up" to the environment and the examiner, the four events were presented to the infant. As in previous research using elicited imitation [17], each imitation task consisted of a baseline phase during which the infant was allowed to manipulate the props for that task with general prompts given (i.e, "what can you do with this stuff?"). This phase serves as a control for general problem-solving skills and motor abilities. Following the baseline phase, the examiner performed narrated modeling of the sequence twice in succession, and the infant was then encouraged to imitate prompted by a defined verbal reminder (see Supplementary Table 1, online). In the immediate imitation condition, the infant was allowed to imitate immediately after watching the examiner, whereas in the delayed imitation condition a 10-min delay was imposed before the infant was permitted to imitate. The 10-min delay was "filled": the baseline and modeling phases of the delayed imitation tasks were presented first, followed by the baseline, modeling, and recall phases of the immediate imitation tasks, and then finally by the recall component of the delayed imitation tasks. See Supplementary Table 2, online, for schematic of experimental design.

### Scoring

Infants were videotaped during the imitation tasks and coded off-line by trained observers who were unaware of the infants' group assignment. For each task, the number of

individual target actions (maximum two per task) and the number of correctly-ordered pairs of actions (maximum 1 per task) was recorded. In assessing ordered pairs, only the first occurrence of each target action was considered, to reduce the likelihood of infants receiving credit for producing a correct sequence by chance.

### Missing data

In two cases (both controls), data was not usable due to malfunction with video recording. These data points were coded as missing and excluded from analysis.

### Bayley scales of infant development

In order to assess overall neurodevelopment, the Bayley Scales of Infant Development–3rd edition (BSID-III) was administered to infants at the 12-month visit. Cognitive, language, and motor subscores were collected for each infant.

## Statistical analysis

Descriptive statistics are shown as mean (SD) or count (percentage), as appropriate for baseline characteristics. Differences in baseline characteristics between the NE and control groups were evaluated using two sample t-test (continuous variables) and Fisher's exact test (categorical variables). Linear regression was performed to assess between-group differences controlling for age and race for VEP latencies, EI scores and Bayley scores. Immediate and deferred recall scores in EI were statistically adjusted for the corresponding baseline score. Pearson correlation coefficients were calculated to assess the relationship between the latency to P2 (an ERP component assessing the speed of the attentional response to an auditory stimulus) in newborns[15] and latency to P100 in 8-month-old, and between the size of the difference wave in newborns (an ERP component measuring the robustness of recognition memory) and EI scores. Within the NE group, VEP latencies and EI scores were compared based on presence or absence of seizures in the neonatal period, MRI findings (normal vs. abnormal), and EEG findings (normal vs. abnormal). All analyses were performed using SAS (v9.3; SAS Institute, Cary, NC). Statistical significance was defined as $p < 0.05$.

## Results

Sixteen infants with moderate NE and 23 controls were included. Comparisons between the groups revealed that control infants had higher Apgar scores, were more likely to be white, and had higher mean maternal age (Table 1). Among the infants with moderate NE, 7/16 (43.7%) had abnormal brain MRIs, 6/16 (37.5) had abnormal aEEG, and 5/16 (31.25%) had documented seizures.

**Table 2** VEP latencies (msec), EI scores, and BSID scores by group

| | Average (SE) | | *P*-value |
|---|---|---|---|
| | NE | Control | |
| VEP: Latency to P100 | | | |
| Left | 150.16 (7.93) | 137.82 (9.99) | 0.26 |
| Midline | 137.06 (7.71) | 141.72 (9.71) | 0.66 |
| Right | 139.42 (7.68) | 151.09 (9.68) | 0.27 |
| EI scores | | | |
| Baseline components | 0.49 (0.11) | 0.64 (0.15) | 0.35 |
| Baseline pairs | 0.02 (0.02) | 0.07 (0.03) | 0.19 |
| Immediate components | 1.13 (0.14) | 0.98 (0.18) | 0.46 |
| Immediate pairs | 0.15 (0.08) | 0.14 (0.10) | 0.90 |
| Deferred components | 0.88 (0.12) | 0.89 (0.15) | 0.95 |
| Deferred pairs | 0.08 (0.07) | 0.18 (0.09) | 0.33 |
| Bayley scores | | | |
| Cognitive | 105.63 (3.29) | 111.01 (4.14) | 0.26 |
| Language | 86.27 (3.72) | 93.07 (4.68) | 0.20 |
| Motor | 94.76 (4.17) | 98.46 (5.25) | 0.53 |

*Note*: VEP latencies and EI scores are adjusted for maternal age and race, and infants' age at time of assessment. BSID scores are adjusted for maternal age and race

## Speed of Processing

Thirteen infants with NE and 19 controls had acceptable VEP data. Table 2 shows the mean latencies to P100 at left, right, and center for each group. After statistically controlling for race and infants' age at the time of the visit, the NE group and control group had similar latencies to P100. Among the NE group, latency to P100 did not differ significantly between those with normal vs. abnormal MRI or EEG, or based on presence or absence of seizures. Among the NE group, latency to P2 (attentional response to auditory stimulus) in left and center leads during the newborn ERP task (in which infants were presented with a novel voice) was positively correlated with latency to P100 on the left in the 8-month VEP task. Fig. 2 shows scatterplots of latency to P2 (newborn) against latency to P100 (8-month-old). There were no statistically significant correlations between latencies in other leads, or in the "familiar" condition of the newborn ERP task (during which infants were exposed to their mother's voice rather than a stranger). Control infants also showed no correlations between latencies from the neonatal period to 8 months of age.

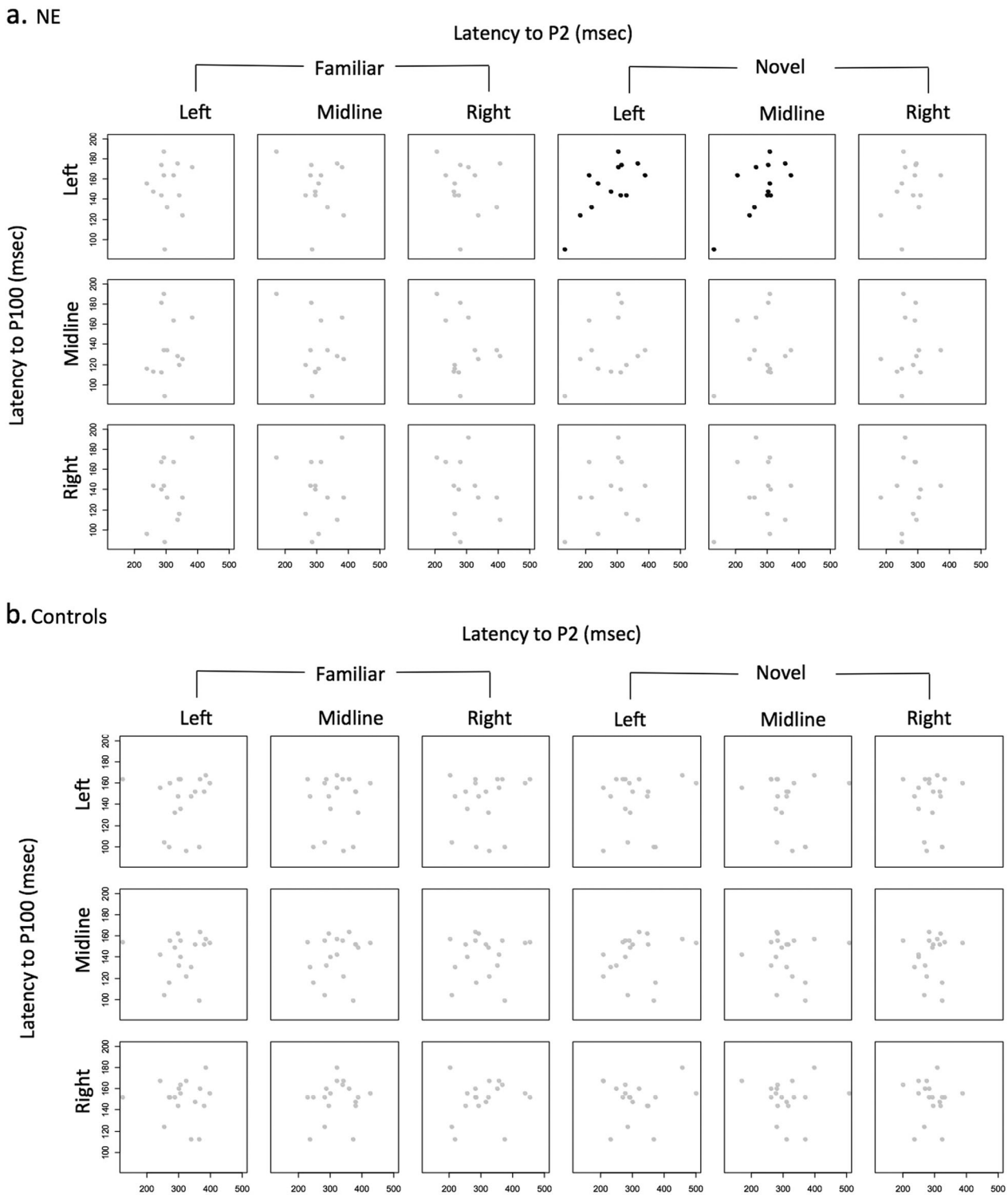


**Fig. 2** Scatterplot showing relationship between latency to P2 in newborns and latency to P100 in 8-month-olds. **a** NE group. **b** Control group. Significant correlations are shown in black

## Elicited imitation and Bayley scores

Fifteen infants with moderate NE and 23 controls returned for the 12-month follow up visit. Elicited imitation was not able to be scored for 2 controls due to a video recording error, so 15 NE and 21 control infants were included in analysis. Table 2 shows average number of correct components and pairs for each group, at baseline and with

immediate and delayed imitation. Infants with NE performed similarly to controls, both with immediate imitation and after a delay. For the NE group, scores did not differ significantly based on MRI, EEG, or seizure status. The size of the difference wave on newborn ERP (an index of memory function) was not correlated with EI performance at 12 months (correlation coefficients ranged from −0.3603 to 0.234, and $p$-values ranged from 0.119 to 0.919).

Scores on the Bayley Scales of Infant Development, 3rd edition (BSID III) are shown in Table 2. The NE group performed equally well as the control group after adjusting for maternal age and race. Among all participants (NE and controls), both cognitive and motor subscores were positively correlated with elicited imitation scores. The Pearson correlation coefficient (r) for the association between baseline EI score and cognitive BSID subscore was 0.397, $p = 0.013$. For the association between baseline EI score and motor BSID subscore, $r = 0.490$, $p = 0.002$. In the immediate imitation condition, cognitive ($r = 0.355$, $p = 0.029$) and motor ($r = 0.350$, $p = 0.031$) subscores were also correlated. The association was not as strong for deferred imitation although there was still a trend toward significance for cognitive subscores ($r = 0.281$, $p = 0.087$).

## Discussion

Children with a history of neonatal encephalopathy are at risk for developmental delays. This study showed reassuring preservation of specific brain functions in a cohort of survivors of moderate NE after therapeutic hypothermia. We chose to focus on infants with moderate NE, since this is where the greatest prognostic uncertainty lies—most children with mild NE have normal cognitive abilities or only mild disabilities, while those with severe NE almost always have some obvious deficits. However, among children with moderate NE there is a wide range of outcomes.

Other studies have shown that therapeutic hypothermia improves outcomes in survivors of NE into middle childhood [8–11]. However, most of these studies have focused primarily on mortality, overall IQ, and sensory/motor impairments, and were not designed to detect more subtle deficits such as impairments in memory or speed of processing, which are important later in childhood for optimal learning and school performance. Two of the trials did include some additional assessments of specific cognitive functions at 6–7 years of age: the TOBY trial assessed memory and processing speed [8], and the NICHD trial assessed attention and executive function [10]. In both of these studies, there were no significant differences in measures of these cognitive functions between the hypothermia and control groups, although the authors acknowledge that the studies were powered to detect overall disability and were not designed to detect these specific impairments. Early detection of such impairments allows for greater response to interventions due to the greater plasticity of the brain in the first 2 years of life.

In this study, infants with a history of moderate neonatal encephalopathy had similar speed of neuronal processing as healthy controls at 8 months of age. While we did not observe a between-group difference, we did observe that speed of processing in the NE group tended to be consistent over time—that is, slower speed of processing in newborns to a novel auditory stimulus correlated with slower visual speed of processing at 8 months. This suggests that damage done to the brain very early in life resulting in impaired processing speed persists at least through 8 months and may or may not ultimately be fully repaired. A study done by Michalczuk et al. showed that in preterm infants, low Apgar scores correlate with longer VEP latencies at school age. The authors suggest that in the preterm population, perinatal damage and an infant's condition at birth influence electrophysiologic responses [19]. Whether or not the slower speed of processing seen in some members of this cohort will persist and have a negative impact on behavior long-term remains to be seen. If it does, newborn ERP could become a useful prognostic test, in addition to currently used prognostic tools such as MRI, EEG, and neurologic exam.

At 12 months of age, episodic memory function was also similar between the groups. Subjects in both groups showed improvement in performance with imitation as compared to baseline, indicating that they learned from observation and retained this information after a ten minutes delay. This finding was consistent with and provided longitudinal confirmation of our previously reported results, in which 2-week-old infants with NE showed preserved ability to discriminate between familiar and novel voices as measured by ERP [15]. While an uncooled NE control group would be necessary to definitively prove that TH improves memory outcomes, when placed in the context of the pre-hypothermia literature showing impaired memory function in survivors of NE [11, 12], our results suggest that therapeutic hypothermia improves not only overall intellectual function, but also memory, and that memory function can be assessed accurately soon after the therapeutic course.

As previously reported [15], the NE and control groups had Bayley scores that were not statistically significantly different after controlling for race and maternal age. Among all participants (both NE and controls), cognitive and motor, but not language, subscores were positively associated with elicited imitation performance. This finding makes intuitive sense, since infants with better motor performance are likely to be better able to physically manipulate the props, and those with more advanced cognitive skills would understand and remember the sequence of actions with more

proficiency. Conversely, as elicited imitation is intentionally designed to test memory function in pre-verbal children, it is not surprising that language scores were not associated with performance.

Interestingly, in this cohort of children with moderate NE, neonatal MRI and EEG findings and presence or absence of seizures in the newborn period were not predictive of outcome at 8 and 12 months of age. Unfortunately, our small sample size prevented us from being able to assess outcomes based on specific patterns of injury on MRI or EEG, and it is certainly true that there are some findings on MRI and EEG that are strongly associated with poor outcomes. However, for those infants with subtler imaging and electrographic abnormalities, our findings indicate that clinicians should be cautious when using these assessments to counsel families about predicted outcomes.

One major strength of our study was the longitudinal study design, in which we were able to follow participants over time and compare results of electrophysiologic and behavioral tests at different stages of infants' development. In particular, the assessment of memory and speed of processing by ERP in the immediate postnatal period shortly after their perinatal encephalopathy is something that has not been done in other studies of survivors of NE.

A significant limitation of our study is the small sample size, which limits the power to detect between-group differences. However, other studies have used similar sample sizes and have been able to detect statistically significant differences in VEP latencies[18] and EI scores [17] in this age group. Another potential limitation is that some baseline characteristics differed between groups. Infants in the control group were more likely to be white and had mothers who were older at the time of delivery. These and other sociodemographic factors are known to affect development [20, 21], although we did control for these differences in the statistical analysis. Additionally, infants in both groups had parents with higher than average levels of educational attainment, which could partially account for the generally reassuring results in this cohort and limit applicability to a broader population. Another difference between groups was the altered ex utero environment experienced by the NE group due to their NICU stay. The length of hospitalization for our participants was relatively short (<2 weeks on average), as compared with preterm infants who may spend months in the NICU, are at a different phase of brain development during their stay (prior to term), and on whom much of the research regarding the effects of NICU hospitalization on brain development has been conducted [22].

While ERP and EI are powerful tools with which to assess memory and other cognitive processes in pre-verbal infants, it is possible that more subtle deficits will become apparent as the children mature and cognitive demands increase. Adaptive changes in brain connectivity that result in the appearance of normal function at 12 months of age can form the basis for abnormal scaffolding leading to inefficient processing and impaired function later in life as cognitive demands become more complex. Our group is currently conducting a follow-up study of the same cohort of children at 4–5 years of age, which may shed additional light on this question.

## Conclusion

This study showed similar speed of neuronal processing, memory function, and general development between infants with moderate NE who underwent therapeutic hypothermia and healthy controls. While memory function in the newborn period was not predictive of developmental outcome at 12 months, slower speed of processing in newborns was associated with slower speed of processing at 8 months in NE group. Further study is needed to assess whether speed of processing correlates with behavioral outcomes in this population. If it does, newborn ERP may be a useful prognostic tool for infants with NE.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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